

Physical Stability of Dry Powder Formulations Studied One Particle at a Time

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Summary

Throughout this project, the long-term physical stability trends of dry powder formulations will be investigated, for delivery using dry powder inhalers (DPI). The focus of this project is to study the stability trends of pharmaceutical blends for dry powder formulations, particularly the long-term physical stability regarding water absorption. The long-term stability of the formulations will be determined by standard protocols which will be compared with measurements of the relative humidity response of individual particles by measuring the change in mass (resolution of 2 pg) and phase in an electrodynamic balance (EDB). The resulting mass change can be converted, to allow a comparison to be made from the rate of water uptake that these particles experience.

Key Message

This research outlines a method to measure the change in mass of single particles when exposed to an environment of a specific relative humidity. The technique allows mass changes as small as 2 pg to be measured.

Introduction

There is great utility in the use of pharmaceutical drugs delivered via the pulmonary route, due to the possibility of localised administration to the lungs for treatment of respiratory disease, or as an alternative delivery route to reach the systemic circulation rapidly. Localised drug delivery to the lungs typically allows lower dosages to be used when compared to, for example, oral dosage forms (tablets, capsules). This can help maintain drug efficacy but reduce unwanted side effects. Within the aerosolised powder for inhalation, there are a large proportion of API particles in the size range of 2 μm – 5 μm . This is desirable as particles smaller than 5 μm have the best probability for deposition within the deep lung, without impaction occurring higher up in the mouth and throat [1]. The deposition of particles within the lung is affected by the size, shape, mass, hygroscopicity and morphology of the particles [2]. There are three main processes for drug deposition: inertial impaction, sedimentation, and diffusion [3].

Dry powders can be used to deliver active drug particles for both local and systemic treatment via a pulmonary route, which is desirable as it allows for the direct delivery of drug particles into the lungs, using a patient's respiration as the driving force. These dry powders are often delivered in two main forms, either as (i) loose agglomerates of micronized particles or (ii) as mixtures of carrier-based systems, where micronized drug particles are adhered to the surface of a carrier particle [1], [4].

The amorphous content of dried powder particles can be induced in the manufacturing of a pharmaceutical system. The presence of amorphous content can also affect manufacturing, stability, bioavailability and therapeutic performance, due to an increase in dissolution rate [5]. Many pharmaceutical drugs are in crystalline form. The processing of pharmaceuticals might introduce amorphous content to an otherwise crystalline structure. However, amorphous state can be introduced purposefully to increase bioavailability/biopharmaceutical properties of the pharmaceutical. Absorbed water can plasticise amorphous solids, therefore, relative humidity (RH) has an influence on solid state properties of amorphous systems [6]. Amorphous materials have a thermodynamic tendency to crystallise. All of these considerations could have an impact on the stability trends seen for pharmaceutical compounds, affecting the size distribution and therefore the performance of the dry powder as time progresses [7].

Experimental methods – Single Particle Electrodynamic Trapping (SPET)

SPET allows the study of time-dependent changes in the physiochemical properties of a suspended aerosol particle, such as particle mass, size and chemical composition [8], [9], [10], [11]. SPET contains a pair of concentric electrodes, which levitate a charged particle within an electrodynamic field. The SPET used in this work has an open-air design and the ability to reach supersaturated conditions in RH. The SPET can also suspend both liquid and solid particles [12].

The RH of the environment is controlled by two air flows, one of dry nitrogen, and one of wet nitrogen. The ratios of dry and wet air can be altered to expose the particles to certain RH conditions.

Once the particle or droplet is suspended in the trap, it is illuminated with a 532 nm laser. The elastic light scattering forms a diffraction pattern that is collected by the cameras and can be used to estimate the size of a solution droplet or identify the phase of the trapped particles. Further, as the particle changes mass via evaporation or condensation of water, the change in mass can be monitored through a change in the DC offset of the bottom electrode. This change occurs to maintain the particles' vertical position within the trap. With calibration, this change in DC offset can be used to determine the change in particle mass.

Results - Determining mass change of particles using SPET

To calculate the mass change in solid particles when they absorb water, the mass balance or DC offset change needs to be calibrated. To calibrate the instrument, a slowly evaporating liquid was used, a solution of decanol in water and ethanol. Once the droplet was stable and no longer moving in the centre of the electrodes, the DC offset was then turned on, which changed the DC offset on the electrodes to keep the droplet in the centre of the electric field, combating the effect of gravity on the droplet. As the droplet evaporated and lost water and therefore mass, the DC offset adjusted to keep the droplet steady, meaning that the evaporation of the droplet can be accurately studied over time as it evaporated. The change in mass is taken as a rate of water loss over time and not as a definitive measurement of the total mass that the droplet loses. From comparing the rate of evaporation for different sized droplets at different frequencies, a calibration curve can be determined, which allows a conversion constant from DC offset change to mass change to be achieved.

To test whether the system can detect a change in mass of solid particles, some preliminary tests were conducted. To begin, this involved seeing if there was any change in the DC offset over time for fine lactose particles when suspended in an air flow of a specific relative humidity (90%). As can be seen in Figure 1, for various fine lactose particles, a change in the mass can be determined. Deciding if the mass of water added to the particles was feasible was confirmed.

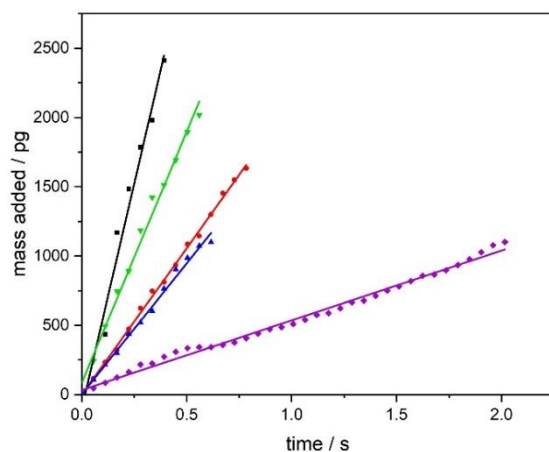


Figure 1 – Preliminary data showing that the mass change for LH210 particles can be determined, RH set to 90%.

Lactose samples testing

Samples of coarse lactose (LH206) and fine lactose (LH210) are investigated. LH206 has a d50 of 83 μm and LH210 has a d50 of 16 μm .

LH206 and LH210 were investigated for the rate of water condensation or rate of water uptake differences across samples. The rate of water uptake is normalised for an approximate size of the particle. It is not the maximum amount of water uptake that the particle experiences as the mass balance within SPET is too sensitive to cover the whole mass change range. The size of the particles is normalised using the average light scattering intensity output.

LH206 vs LH210

Comparing the water uptake for samples of coarse (LH206) and fine (LH210) lactose samples investigated using SPET, can be seen in Figure 2. The mean of the data is highlighted by the grey circles. Each point represents the water uptake per second for that lactose particle.

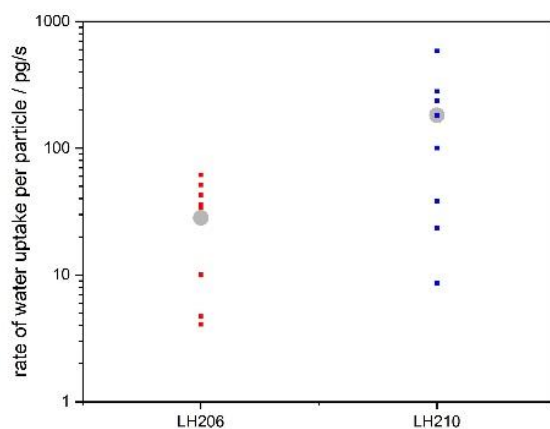


Figure 2 – Comparing mass of water uptake per second onto particles of LH206 and LH210, RH set to 40%.

When comparing the data sets, a clear difference between the two mean values can be seen, once normalised by particle size. This suggests that the LH210 contains a higher proportion of amorphous content in comparison to LH206. The fact that LH210 takes up water more quickly means that there must be more amorphous content to take up water from the gas phase, assuming the crystalline phase does not take up water because the RH here of 40% is well below the deliquescence point for lactose which is found to be between 87% and 99% [13]. There is considerable variation from particle to particle. Indeed, assessing this variability is one of the key objectives of the experiment as it allows the variability across individual particles to be assessed. The variability likely arises from variations in particle mass and surface area and amorphous content. Although particles are all trapped with the same trapping voltage, suggesting they should all be of similar mass-to-charge ratio, the level of charge imparted to the particles may vary and the mass selection is not monodispersed. Future work will identify and assess more fully the source of this variability.

It was promising to see a large difference in the means of the distribution of the separate particles as it suggests that the differences from different particles can be seen. The variability in the particles for the same particle type, e.g. LH206, could be due to the differences from particle to particle. Particles in a similar section of the size distribution are observed, as a set voltage is used to trap particles of a similar size. This could include different amounts of amorphous content within the particle, different mass of the particle, different morphology or differing surface areas.

The plots are shown on a log scale, to bring them onto the same scale, this does however, make the means appear more similar in comparison. A p-value for the data sets provide a value of 0.04, this suggests that the data sets shown are statistically significant.

LH206 vs Blended LH206

It is important to see if a difference between the materials before and after blending can be seen. This would confirm if the process of blending the powder did in fact cause changes to the raw material. The comparison between LH206 and blended LH206 can be seen in Figure 3.

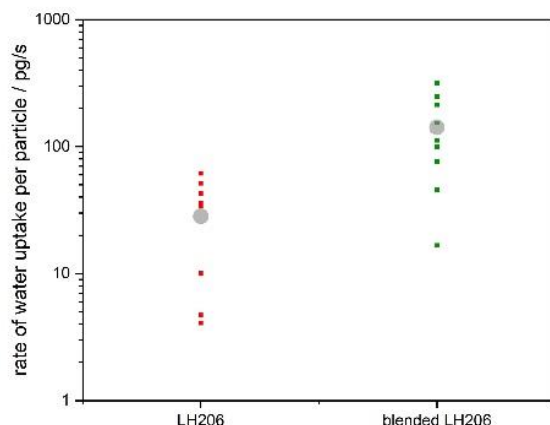


Figure 3 – Comparing mass of water uptake per second on particles of LH206 and a sample of blended LH206, RH set to 40%

The blended LH206 has a higher mean uptake of water for each particle. This comparison allows an observation about the effect on blending particles to be made. The same batch of LH206 particles were used for this comparison, a sample was blended, and a sample was not. The comparison of these two samples shows a higher uptake of water for the blended sample. This confirms the assumption that amorphous content is likely to be formed in the blending process.

Conclusion

This research shows that mass changes can be seen in different types of lactose particles. Small changes in mass can be seen in both LH206 and LH210, as well as blended particles. The preliminary data suggests promise for determining differences in dry powders as time progresses to analyse changes in the water absorption.

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